REMARKS

Claims 14 and 16-22 are pending in this application.

Rejection under 35 U.S.C. 103

The Examiner rejects claims 14 and 16-22 as unpatentable under 35 U.S.C. 103(a) over Delgado *et al., British J. Cancer* 73:175-182 (1996) in view of U.S. Patent 5,714,142, WO 98/00171, U.S. Patent 5,670,132 and Peters (that was previously encountered).

I. The Examiner's Position

A. The prior art

According to the Examiner, Delgado *et al.* teach that F(ab')2 fragments of monoclonal antibody F9 are currently the most promising agent in clinical trials (*see, e.g.* page 180, column 2) and that Fab fragments are less effective. Further, Delgado *et al.* allegedly teach coupling PEG to the F(ab')2 fragment thereby making a molecule having increased specificity for tumors and increased plasma half life. Moreover, such molecule allegedly exhibits less antigen binding and is useful for drug delivery and for tumor imaging. The Examiner admits that Delgado *et al.* do not teach an antibody fragment coupled to position 34 of albumin through a bridging agent of from 10-20 Angstroms according to the present invention.

The Examiner says that U.S. Patent 5,714,142 teach that albumin may be conjugated to small molecule drugs, peptides or proteins to increase half life of the same. Further, the '142 patent allegedly discloses linker molecules such as an optionally substituted alkylene (e.g. hexylene at Column 6) and that the active agent should be capable of derivitization without significant loss of activity (see, e.g., Column 13, lines 55-66). Hence, the active agent should be bound by a functional group or side chain not essential for pharmacological activity.

The Examiner maintains that WO 98/00717 teaches conjugates of drugs covalently coupled to blood components such as albumin via a linking polypeptide or alkylene of 6 carbon atoms through groups including thiol groups. Allegedly, the reference teaches that by coupling the drug to albumin, the activity of the drug is extended, the half life of the drug is increased, and greater specificity is produced.

The Examiner contends that U.S. 5,670,132 teaches PEG-coupled-TC-99m-radiolabeled antibody fragments that are useful for radioimmunodetection of tumors and that the exemplified antibody fragments display faster targeting kinetics and are not as immunogenic as intact antibody molecules. Further, the '132 patent allegedly teaches using the disulfide bonds in the hinge region of the antibody fragments to couple a label to the antibody fragments and that the coupled molecule retains its ability to bind antigen. In addition, the Examiner says that the '132 patent teaches that for imaging using bivalent F(ab')2 fragments, it is necessary to either partially reduce interchain disulfide bonds without further cleaving the fragment or to thiolate the fragment (*see, e.g.* Column 4, lines 47-67 and Column 5, lines 1-15).

According to the Examiner, Peters teaches that free cysteine is present in albumin (see, e.g. paragraph bridging pages 164-165).

B. Alleged *prima facie* case of obviousness

The Examiner maintains that it would have been obvious to **1) subsitute the PEG** of the antibody fragment of Delgado *et al.* **with the albumin** of the '142 patent and WO 98/00717. Moreover, it would have been obvious to have **2) linked the antibody fragment to albumin using a linker such as an optionally substituted hexylene** as taught by the '142 patent **or the 6 carbon alkylene** linker of WO 98/00717. Further, such linker would have been **3) linked via the thiol at the free cysteine in albumin** as taught by Peters, and the thiols would have been created as per the '132 patent to have **4) optionally linked the conjugate to a label** (in effect the reporter group of claim 19 of the present application).

C. Motivation to make such changes

The Examiner contends that **1)** one of skill in the art would have been motivated to **increase the efficacy of drug delivery or tumor imaging** by increasing antigen binding capacity and half life of a subject antibody fragment by linking it to albumin via a linker. The Examiner adds that **2)** the '142 patent and WO 98/00717 teach proper linkers (optionally substituted hexylene or 6 carbon alkylene). Moreover, the Examiner adds that **3)** Peters teaches free cysteine in albumin and that it would be **obvoius to couple albumin at this cysteine**

because this cysteine is available without requiring manipulation or causing a conformational change in albumin. Further, the Examiner maintains that **4)** the '132 patent teaches that **reduced cysteine residues (i.e. thiol) in the hinge region of antibody fragments may be used to label antibody fragments**.

Regarding the recitation entered in the last Amendment,

> *"wherein the antibody fragment and albumin are indirectly linked by a bridging molecule of from around 10A to 20A in length between the thiol groups of a cysteine residue present in the antibody and another present in the albumin at position 34,"*

the Examiner says that the optionally substituted hexylene of the '142 patent or the 6 carbon alkylene linker of WO 98/00717 meet this length limitation.

The Examiner adds that as regards claim 17, it would have been obvious to extend the fab at the CH1 carboxy terminus to include the cysteine involved in the interchain disulfide bond of theintact antibody in order to utilize the cysteine in disulfide binding without disrupting intrachain disulfide bonds. The Examiner says that the '132 patent discloses introducing additional thiol groups to the antibody fragments.

II. Applicant's Response

A. The Examiner has not set forth a proper *prima facie* case of obviousness

1. The primary reference is remote from the claimed invention

Delgado *et al.* teach antigen binding antibody fragments covalently linked to PEG to increase plasma half-life. The only common feature between Delgado and claim 14, presently pending, is the presence of the antibody fragment. The Examiner alleges, however, that it would have been obvious to:

1) replace the PEG in Delgado with albumin in view of the disclosure of linking albumin to molecules in WO98/00171 and US5,714,142;

2) link the albumin to the antibody fragment using a bridging molecule of 10 to 20Å in length in view of the disclosure of linkers of this length in WO98/00171 and US5,714,142; and
3) link the bridging molecule via the cysteine residue present in albumin at position 34 in view of the disclosure in Peters of a free cysteine in albumin.

2. The legal requirements for a prima facie case of obviousness

Applicants respectfully remind the Examiner that in order to establish a proper *prima facie* case of obviousness, the Examiner must establish certain criteria as follows:

1. That there is a suggestion or motivation to modify the references or to combine the reference teachings;
2. There must be a reasonable expectation of success; and
3. The references or combination of references must teach or suggest all of the claim limitations (*see, e.g.,* MPEP § 2142).

The teachings or suggestions to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cr. 1991)). The arguments advanced by the Examiner fail to meet all of these criteria.

The law is settled that prior to combining references for the purpose of determining obviousness, "there must be some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art that would lead that individual to combine the relevant teachings of the references." *See, In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The law is also settled that "the prior art references must be evaluated on what they taught or suggested...when the invention was made, not on hypothetical modifications made with knowledge of the invention..." (*See, e.g. Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985) The Examiner's rejection appears to be based purely on hindsight, and hindsight has never been permissible to establish a *prima facie*

case of obviousness. The fact that the Examiner is combining sections from no less than four documents to arrive at the subject-matter of claim 14 demonstrates, in itself, that the invention is not obvious as the Examiner alleges. Furthermore, the Examiner's allegation that motivation to combine these documents exists within the documents is incorrect, as shown by the detailed review of the documents provided below.

B. The Prior Art

1. Regarding Delgado *et al.*

The introduction of Delgado *et al.* teach that covalent modification of proteins with PEG is known to increase the plasma half-like of protein therapeutics in general and has been suggested as a useful tool for improving the half-life of therapeutic antibodies. Delgado *et al.* go on to note that they have developed an improved method of directly linking PEG to proteins. The improved method was used to modify a recombinant chimeric F(ab') fragment of an anti-tumor antibody termed F9, and the biological properties of the resulting conjugates were assessed.

The results showed that coupling F9 to several PEG molecules resulted in an extended plasma half-life as a result of reduced renal clearance. The PEGylated F9 had reduced antigen binding compared to the non-PEGylated antibody but, despite this, an increase in tumor specificity was observed. Delgado *et al.* suggest that the reduced antigen binding might therefore be beneficial in achieving improved tumor uptake (*See, e.g.,* page 180, second column, third paragraph).

Delgado *et al.* thus achieved what they set out to do, namely, to improve plasma half-life of an antibody fragment by reducing renal clearance. Contrary to the Examiner's assertion, Delgado *et al.* provide absolutely no motivation to one of ordinary skill in the art to make changes to the construct taught therein. Certainly, Delgado *et al.* provide absolutely no motivation to replace the PEG moieties with an albumin molecule. Likewise, there is no evidence among the teachings of Delgado *et al.* or among the literature that albumin would have the same properties as PEG, *i.e.* reduced renal clearance and improved tumor localization. One of ordinary skill in the art would have had no desire to replace the PEG in the antibody Fab'

fragment provided by Delgado *et al.* with albumin in case this affected antigen binding and tumor localization. As there is neither a teaching of albumin nor any motivation in Delgado *et al.* to use albumin, there is certainly no motivation to use a bridging molecule of from around 10Å to around 20Å in length to link a cysteine at position 34 of albumin to the antibody fragment.

2. Regarding U.S. Patent 5,714,142 ('142)

The background introduction of the '142 patent describes proteins which have had their half-lives extended by conjugation to human serum albumin. The '142 patent is, however, concerned with solving the problem that drugs conjugated to serum albumin *in vitro* are too large to be orally absorbed and must be administered by injection. The '142 patent solves this problem by providing ligands that bind an endogenous plasma protein, transthyretin (TTR), also known as prealbumin. ***The TTR protein is structurally unrelated to albumin.*** The TTR ligands are conjugated to a drug, resulting in a drug-TTR ligand which is small enough to be orally adsorbed. Following oral administration, the conjugate binds to TTR *in vivo,* resulting in an increase in the half-life of the drug.

Possible drugs to which the TTR ligands may be conjugated are listed in columns 4 and 14. Antibody fragments are not mentioned in this list.

The '142 patent does not therefore teach an antibody fragment-albumin conjugate. Instead, the '142 patent teaches drug-ligand conjugates in which the ligands bind to a completely different serum protein, TTR, *in vivo*. The disclosure of the '142 patent is not therefore relevant to claim 14. The '142 provides absolutely no motivation to conjugate an antibody fragment to albumin via a bridging molecule at position 34 of albumin. Quite to the contrary, ***the '142 patent teaches against conjugating drugs to albumin*** on the basis that the resulting conjugates are too large to administer orally.

3. Regarding WO98/00171

WO98/00171 is concerned with extending the half-life of chemical inhibitors of thrombin activity in a mammalian host. The thrombin inhibitors are compounds that have a chemically

reactive group which reacts with available "reactive functionalities" on various blood components.

Albumin is listed on page 5, last paragraph, of WO98/00171 as only one of more than 10 possible blood components with which the thrombin inhibitors may react. WO98/00171 lists thiol groups as only one of three possible reactive functionalities on the blood components with which the thrombin inhibitors may interact. (See, page 8, first paragraph) Amino groups are stated to be the preferred reactive functionalities for interaction and, in the Examples, where a thrombin inhibitor is attached to albumin, the attachment is effected via the carboxyl moiety of an ester on the thrombin inhibitor which reacts with amino groups in albumin to form an amide bond.

WO98/00171 is only concerned with extending the half-life of chemical thrombin inhibitors, not antibodies. WO98/00171 is certainly not concerned with site-specifically linking an antibody to albumin at a specific cysteine residue. WO98/00171 merely provides a long list of linkers suitable for attaching a thrombin inhibitor to any one of a long list of blood components including proteins and cells. (See, page 7) There is no indication that these linkers would be suitable for linking antibody fragments to albumin.

In the Examples, random multiple attachment of the thrombin inhibitors to amino groups on the albumin had no detrimental effect on the biological activity of the thrombin inhibitor. WO98/00171 therefore provides no motivation for the skilled person to seek alternative approaches, including attaching antibody fragments to a single, specific site on albumin using a linker of around 10Å to around 20Å in length.

In summary there are four main differences between WO98/00171 and claim 14 as follows:

1. WO98/00171 concerns thrombin inhibitors, not an antibody fragment;
2. Albumin is only one of many examples of blood components to which the thrombin inhibitors may be conjugated;
3. Thiol residues are only one of many possible sites of attachment between the thrombin inhibitor and albumin; and

4. There is no teaching or suggestion to use the cysteine residue at position 34 of albumin as the site of attachment between the thrombin inhibitor and albumin.

4. Regarding Peters

Peters reviews the biochemistry of albumin, its properties and structure. There is absolutely no teaching or suggestion within Peters of antibody fragments and the conjugation of albumin to such fragments.

5. U.S. Patent 5,670,132 ('132)

The '132 patent describes PEG-modified-Tc-99m-radiolabeled antibody fragments. The PEG is used to significantly reduce the renal uptake compared to a non-PEGylated antibody fragment. The PEG moiety and/or radiolabel may be attached to the hinge thiols of antibody fragments.

The '132 patent does not describe conjugation of antibody fragments to albumin. It provides no motivation to replace PEG with albumin as the use of PEG is successful in reducing renal uptake (*See,* Example 10) or to use a linker of around 10Å to around 20Å in length to do so.

C. No motivation to combine references

In view of the content of the cited references discussed above, it is apparent that the skilled person would have had no motivation to combine the references in the manner suggested by the Examiner.

1. No motivation to replace PEG with single albumin

There was no problem associated with attaching several PEG molecules to an antibody fragment in Delgado *et al.* or the '132 patent. The approaches described therein were apparently successful and there would have been no motivation for replacing PEG with a single albumin.

Importantly, there is no evidence or suggestion in any of the references cited, in particular the '142 patent and the '171 patent, that substituting PEG for albumin would increase the 'antigen binding capacity' of an antibody fragment as asserted by the Examiner. The '142 patent is concerned with linking drugs to TTR *in vivo,* not with covalently conjugating albumin to an antibody fragment *in vitro*. The '171 patent makes no reference to antibodies but relates to randomly attaching several thrombin inhibitors to albumin.

2. ***No motivation to use linkers in '142 or '171 to attach albumin to an antibody fragment***

The linkers disclosed in the '142 patent are designed to ***link a drug to TTR, not albumin***. Furthermore, the linkers disclosed in the '142 patent are designed to link the drug to TTR *in vivo*. A person skilled in the art would therefore not be motivated to use these linkers for the purpose of covalently attaching albumin to an antibody fragment *in vitro*.

The linkers disclosed in the '171 patent were designed to link a thrombin inhibitor drug to *inter alia* albumin and would not have been considered by the skilled person for linking albumin to an antibody fragment.

3. ***No motivation to link antibody fragment site-specifically to albumin***

The '171 patent provides no motivation to link albumin to an antibody fragment via the cysteine at position 34 of albumin. The '171 patent suggests that thiol groups can be used as just one example of various sites of attachment for thrombin drugs to any of the blood components listed but does not go on to use thiol groups in the examples. Instead, amino groups are successfully employed as the site of attachment in the examples. Further, there is ***no suggestion that a single thiol group in albumin should be used***. Indeed, in the examples, multiple drugs are attached to each albumin molecule and there is no motivation to conjugate a single drug to a single albumin molecule.

The '142 patent does not disclose preferably ***coupling a single drug*** to TTR. The '142 patent is concerned with ***random*** conjugation of drugs to ***TTR in vivo***, **not covalent site specific conjugation of antibodies to albumin *in vitro*.**

The Peters reference would not therefore be considered in combination with the '142 patent or the '171 patent as neither of these references provides any motivation to attach a single antibody fragment to a single cysteine in albumin. Further, the Peters reference would not be considered in combination with Delgado *et al.* or the '132 patent as neither of these references refer to albumin or even consider it as an alternative to PEG.

In addition, Applicants submit that it was not *prima facie* obvious, as suggested by the Examiner, to couple albumin through the single cysteine at position 34 because the conformation of albumin would remain unchanged. There is simply ***no teaching or suggestion in Peters that linking an antibody fragment to position 34 of albumin using a bridging molecule of from around 10Å to around 20Å would not affect the conformation of the albumin or that the half-life of albumin would be unaffected.***

In summary

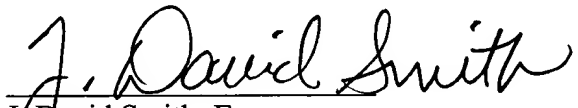
In summary, Applicants respectfully submit that the Examiner is incorrect in maintaining that it would have been obvious to the skilled person to make the major changes to the construct in Delgado *et al.* to arrive at the construct of claim 14. The skilled person would not have been motivated to make the changes suggested by the Examiner. Claim 14 is inventive over the combination of references cited by the Examiner. The remaining claims are dependent on claim 14 and are thus also inventive over the references cited by the Examiner.

Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. § 103 are improper. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and early allowance of the claims as amended is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,



J. David Smith, Esq.
Agent for Applicant(s)
Registration No. 39,839

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, NJ 07601
(201) 487-5800